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# Exercise as a treatment modality for depression: A narrative review ☆

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ABSTRACT

Depression is a major health burden associated with poor quality of life and impaired functioning. Depression is a leading cause of disability worldwide and is associated with profound economic costs. Depression is usually treated with antidepressant medications and psychological therapy or combination of both. However, there are lot of limitations associated with these therapies and as a result, a number of alternative or adjunctive therapies have been sought for. Exercise is one such option with a lot of substantial supportive research. The objective of the article was to review the beneficial effects of exercise in depression. An electronic search of literature from inception till 06/2017 highlighting the effects of exercise on depression and the possible mechanistic pathways involved was conducted using PubMed/Medline, Google scholar and Scopus and relevant articles were utilized for this review. The results of this review confirmed the beneficial role of exercise in depression as evidenced by the improvement in the outcomes and the various psychobiological parameters measured. Thus exercise can be considered as a treatment option for the management of depression.



**Contents**



## 1. Introduction

Major depressive disorder (MDD) is the commonly occurring psychiatric disorder with a life-time prevalence of 15–20% and associated with significant morbidity, mortality and disability.[1] Depression is characterized by fatigue, lack of energy, loss of interest in normal activities, sleep disturbances including insomnia or excessive sleeping, feelings of sadness, tearfulness, worthlessness or guilt etc. The patients with depression often have difficulty in thinking, concentration, making decisions and remembering things.[2] According to WHO (World Health Organization), depression is the leading cause of disability worldwide and is a major contributor to the overall global burden of disease. More women are affected by depression than men.[3] The overall prevalence of

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depression in Europe is 8.5%.[4] In the last decade, the global prevalence of depression is on the verge of increasing.[5] In developing countries, 10 to 44% suffer from depression and anxiety disorders but the medical care is received by less than 35% of the depressed.[6] The prevalence of depression in primary care varies between 15.3 and 22%, with global prevalence up to 13% and between 17 and 46% in Saudi Arabia.[7] The patients with depression are usually treated with medication or psychotherapy or a combination of both.[8] Many of the depressed people do not seek any treatment and hence depression generally remains to be one of the most undertreated conditions.[9,10] Approximately only 12% of the people with depression seek professional help, partly because of the stigma associated with it.[10] Only 18% to 25% of the treated depressed patients in the United States have been reported to receive adequate treatment.[11] The most commonly used treatments being second generation antidepressants.[12] However, patients on antidepressant treatments often experience adverse events and are unable to continue with the treatment.[13,14] Most of the patients on antidepressant medications do not achieve remission after initial treatment[15] and nearly one-third of the patients do not achieve remission even after several treatment steps.[16,17] The patients with depression usually have poor compliance to the medication regimens.[9,18,19] The patients with depression have higher treatment-specific stigma with antidepressant medication than for example with herbal remedies.[20] Because of all these limitations, there is a lot of emphasis on alternative treatment options. Physical exercise (PE) is one such option which has gained considerable attention.[21]

## 2. Methods

An electronic search of literature from inception till 06/2017 highlighting the effects of exercise on depression and the possible mechanistic pathways involved was conducted using PubMed/ Medline, Google scholar and Scopus and relevant articles were utilized for this review. The keywords used for literature search included depression, exercise, physical activity and mechanistic pathways. The studies involving patients with diagnosis of depression were included and studies wherein depression was reported as co-morbidity along with another disease were excluded. Previously published reviews were also referred to. The abstracts and articles published in languages other than English and with incomplete data were excluded.

## 3. Exercise and depression

In clinical setting, exercise interventions are defined as "planned, structured, and repetitive bodily movements done to improve or maintain one or more components of physical fitness".[22] Exercise has less side-effect and can be adapted as per medical co-morbidities and functional status of the patient.[22,23] The self esteem is also enhanced with PE.[24] Exercise is associated with less stigmatization than psychotherapy and the use of pharmacotherapies in MDD can be reduced.[25] Both aerobic and anaerobic (strength training) forms of exercise have been beneficial in reducing depressive symptoms. Some of the aerobic exercise activities include walking, running and cycling or a combination of these. A lot of trials have highlighted the beneficial role of aerobic exercise in reducing depressive symptoms while trials highlighting the beneficial role of resistance training are few.[26,27] As a result; exercise has been included for the treatment of MDD in the American Psychiatric Association's most recent treatment guidelines.[26,28] Exercise has been shown to be beneficial as a stand-alone[29,30] as well as an augmentation treatment[31–33] for MDD. The antidepressant effects of exercise are now well confirmed and can be compared with other empirically supported treatments in mild to moderate depression.[34] A large number of studies and reviews have highlighted the beneficial effects of exercise on depression.[8,27,29–49] The outcomes of few the reports are presented below in brief.

In 2013, Cooney et al.[34] published a Cochrane review, an update of 2009 review by Mead et al.[35] The 2013 Cochrane review consisted of 39 trials of which 37 provided data for meta-analysis. However, there were multiple sourcses of bias in many of the trials; in 14 of the studies randomization was adequately concealed, 15 used intention-to-treat analyses and 12 used blinded outcome assessors. In 35 trials which compared exercise with no treatment or a control intervention, a moderate clinical effect was found (standardized mean difference, SMD: −0.62, 95% CI −0.810 to −0.42). And when only 6 trials with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment were included, the outcome was not statistically significant (SMD: −0.18, 95% CI: −0.47 to 0.11). In eight of the trials providing long-term follow-up (FU) data on mood revealed a small effect in favour of exercise (SMD: −0.33, 95% CI: −0.63 to −0.03). In seven trials, the effect of exercise was compared with psychological therapy and no significant difference was noted (SMD: −0.03, 95% CI: −0.32 to 0.26). In comparison to pharmacological treatment, four trials found no significant difference with exercise (SMD: −0.11, 95% CI: −0.34, 0.12). And one trial reported that exercise was more effective than bright light therapy (SMD: −6.40, 95% CI: −10.20 to −2.60).

A recent study by Olson et al.[45] evaluated the effect of aerobic exercise on cognitive control in major depression (MD). The participants were randomized to an 8-week intervention of aerobic exercise (three sessions/ week of moderate-intensity exercise training) or placebo exercise (sessions/ week of light-intensity stretching). A significant reduction of depressive symptoms was found in aerobic exercise group when compared with the placebo exercise group post 8-weeks of intervention. An improvement in cognitive control processes was also observed. However, the drawback of the study was relatively smaller sample size (undergraduate students) and shorter duration of intervention.

Hallgren et al.[46] carried out a comparative study in 946 patients diagnosed with mild to moderate depression who were randomly assigned to one of three 12-week interventions: group exercise, internet based cognitive behavioural therapy (ICBT) or treatment as usual (TAU). In all the three groups, a significant reduction in depression severity was observed at 12-month FU. However, depressive symptom severity decrease was significant in exercise and ICBT groups when compared to TAU.

Tsuji et al.[47] in a prospective observational study examined the effect of participation in group exercise and regular walking on depressive symptoms among older survivors post the 2011 great east Japan earthquake. The older adults who had more frequently participated in group exercise were significantly associated with lower depressive symptoms. Where as in older adults who did regular walking had marginally significant lower depressive symptoms.

Blumenthal et al.[48] conducted a 16-week randomized clinical trial (RCT) to assess the effectiveness between an aerobic exercise program and antidepressant medication (sertraline hydrochloride) for treatment of MDD. 156 subjects were randomly assigned to a program of aerobic exercise, antidepressant medication (sertraline hydrochloride) or a combination of both. Post 16-weeks, aerobic exercise and antidepressant medication were found to be equally effective in reducing the severity of depressive symptoms, however, a faster initial response was observed with medication group (in the first three weeks). These same subjects were examined by Babyak et al.[49] after 10 months. The results of this examination found lower rates of depression and lower rate of relapse among

subjects in the exercise group than subjects in medication and combined groups. The subjects exercising on own during the FU period were associated with reduced probability of depression at the end of that period.

Chang et al.[50] compared the effects of four different amounts of exercises (3 times a week for 15 min, 3 times a week for 30 min, 6 times a week for 15 min, 6 times a week for 30 min) for preventing depressive symptoms in community-dwelling Taiwanese older adults (aged 65 years and above). The results of the study concluded that all persistent exercise models, even if performed at low amount (3 times a week for 15 min) had significant ameliorative effects on depressive symptoms.

Roh SY.[51] examined the effects of a 16-week pilates exercise program on the ego resiliency and depression in elderly women (n = 148). The questionnaires were used to examine the effects. There was a statistically significant difference in self-confidence, communication efficiency, optimistic trait and anger management. All these sub variables of the ego resiliency of the participants improved compared to their status before participation in the pilates exercise program. A statistically significant difference in depression of elderly woman was observed. The depression of elderly woman radically decreased post exercise program than in the preliminary test.

In a letter to the editor, Jaffery et al.[52] highlighted the outcomes of their study evaluating the effects of acute exercise (5-min bout of walking) on depression and mood profiles using a 4-group Solomon experimental design. An improvement of overall mood profile including depression symptoms post 5-min bout of walking was reported.

Lavretsky et al.[53] conducted a RCT in elderly patients to check the efficacy of complementary use of Tai Chi Chih (TCC) versus health education as an addition to standard antidepressant medication treatment (escitalopram) of depression. Of the one hundred twelve patients recruited, 73 partial responders to escitalopram continued to receive escitalopram daily and were randomized to receive escitalopram and TCC for 2 h per week or escitalopram and health education for 2 h per week. A greater reduction of depressive symptoms was noted in participants receiving escitalopram with TCC when compared with those receiving escitalopram and health education.

A recent randomized trial by Siqueira et al.[54] found that in comparison to a no activity control group, the subjects randomized to a 4-week aerobic exercise program required a lower dosage of sertraline than the subjects in the control group (sertraline monotherapy). The depression severity was significantly decreased in both the groups post intervention.

A bunch of RCTs and meta-analyses have highlighted the benefits of exercise for the management of postpartum depression. The highlight of two of the recent meta-analyses is presented here.

Recently McCurdy et al.[55] conducted a meta-analysis to examine the influence of exercise on depressive symptoms and the prevalence of depression in the post partum period. After a relevant search, 16 articles were utilized for analysis of which 10 trials examined the effects of exercise on treatment and in six trials prevention of post partum depression and depressive symptoms was investigated. Across all the 16 trials, the pooled SMD was -0.34 (95% CI: -0.50 to -0.19), suggesting a small exercise effect on depressive symptoms in all post partum subjects. In 10 of the treatment trials, a moderate effect of exercise (SMD: -0.48, 95% CI: -0.73 to -0.22) was found. In six of the prevention trials, a small effect size of exercise (SMD: −0.22, 95% CI: −0.36 to −0.08) was found. In women with depression, exercise was found to increase the odds of resolving depression post intervention by 54% (odds ratio 0.46, 95% CI: 0.25–0.84). The trials included in the meta-analysis were of smaller size and few had methodological limitations.

Another meta-analysis by Poyatos-Leon et al.[56] evaluated the effect of physical activity (PA) interventions through pregnancy and postpartum period for the management of postpartum depressive symptoms. After a systematic and relevant search, twelve studies were included in this meta-analysis. For PA interventions through pregnancy and the postpartum period versus the control group, a decrease in postpartum depressive symptoms was observed in favour of PA group (effect size: 0.41, 95% CI: 0.28–0.54). A post subgroup analysis, pooled effect size was 0.67 (95% CI: 0.44–0.90) for mothers who met postpartum depressive symptoms criteria at baseline based on specific scales, and 0.29 (95% CI: 0.14–0.45) for mothers who did not meet those depressive symptoms criteria at baseline.

In a prospective interventional trial, El-Rafie et al.[57] evaluated the effect of exercise on antenatal depression. The study involved 100 pregnant women divided into exercise group and the control group. The subjects in the exercise group had regular supervised sessions for 12 weeks plus usual prenatal care. Post 12 week intervention, a significant improvement of the depressive symptoms was observed in exercise group when compared with the control group. Further within groups, a significant improvement of depressive symptoms from baseline to completion of intervention was demonstrated by subjects in exercise group when compared with the subjects in control group.

## 4. Exercise and depression – Mechanistic pathways

The beneficial effects of exercise on depression might be because of multiple possible mechanisms. A number of biomarkers and parameters are altered in patients with depression. Exercise modulates these biomarkers and parameters and results in the improvement of depressive symptoms in the patients. The effect of exercise on few of the biomarkers/parameters is described in brief below.

### *4.1. Effect on neurotransmitters, neurotrophins and neurogeneration*

Exercise has shown to increase the availability of neurotransmitters such as 5-HT, dopamine, and nor-adrenaline in the brain.[23,58,59] Exercise stimulates growth of nerve cells and release of proteins which are beneficial for the health and survival of nerve cells.[37] Brain-derived neurotrophic factor (BDNF) is one such neurotrophic protein has a prominent role in the neuroprotection, neurogenesis, neuroregeneration and synaptic plasticity.[60] The concentration of BDNF is known to be decreased in patients with MDD and is increased with anti-depressant drug treatment.[61] BDNF serves as a growth factor for the hippocampus. Exercise increases concentration of BDNF in patients with depression.[62] There are numerous studies which have shown that exercise enhances levels of BDNF in the hippocampus.[63–65] The higher serum levels of BDNF are associated with larger hippocampal volume.[66] The hippocampal volume is reduced in patients with depression[67,68] and antidepressant treatment allows formation of new cells in the hippocampus.[69] An increase in hippocampal volume and improvement in short term memory was observed in patients who underwent aerobic exercise for 3 months.[70] In a single blind RCT, a moderate intensity aerobic exercise intervention carried out in older adults for one year was effective at increasing the size of hippocampus. The volume of left and right hippocampus was increased by 2.12% and 1.97% respectively.[71] In another study, the subjects were randomized either to a 6 week structured and supervised exercise intervention plus TAU, or to TAU. The TAU consisted to psychotherapy for each patient, plus antidepressant medication. An increase in serum BDNF levels was observed in exercise group compared to TAU group.[62] Like BDNF, putative factor acting

on the hippocampus that might contribute to the positive effects of exercise on mood regulation is orexin-A.[72,73] An increase in the levels of orexin-A was observed in humans post exercise. The post exercise values of orexin-A were considerably higher compared to pre-exercise values.[74]

### 4.2. Effect on pro-inflammatory cytokines

Depression is often accompanied by activation of the inflammatory response[75] system as demonstrated by increased production of pro-inflammatory cytokines (PICs) such as interleukin-1beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) etc.[76–82] The PICs can contribute directly to the development of depressive symptoms.[83] A significantly higher concentration of IL-6 and TNF-α has been consistently found in depression.[75] In another meta-analysis, it was confirmed that elevated levels of IL-1 and IL-6 were positively associated with depression.[84] PE decreases pro-inflammatory mediators.[85,86] In 105 depressed patients, a significant positive correlation between change in IL-1β and higher baseline levels of TNF-α were associated with greater decrease in depressive symptoms following 12 weeks of aerobic exercise intervention.[87] In another RCT, a decrease in IL-6 levels was observed following a 12 week exercise intervention. Improvements in depression severity scores were linearly related to reductions in serum levels of IL-6 and that higher baseline serum IL-6 levels were associated with a stronger treatment response.[88] In another study, aerobic exercise over a period of 10 months was found to reduce pro-inflammatory factors (i.e., C-reactive protein, interleukin-5, TNF-α and interleukin-18) when compared to a combination of flexibility and strength exercise.[89]

### 4.3. Modulation of hypothalamic-pituitary-adrenal axis

The patients with MDD experience hyperactivity of the hypothalamic-pituitaryadrenal (HPA) axis secondary to hypersecretion of corticotropin-releasing hormone (CRH). The increased concentration of cortisol in plasma, urine and cerebrospinal fluid (CSF) are noted in patients with depression.[90] Exercise also activates the HPA axis and increases the levels of cortisol. The cortisol serves as a mediator between chronic stress and depression and is considered to link various cognitive deficits. The basal cortisol levels are elevated in response to both chronic stress and exercise, the former is detrimental to cognition, mood/stress coping, and neural plasticity, while the latter is beneficial.[91] Although acute exercise sharply increases the levels of cortisol, chronic exercise may also increase basal cortisol levels.[92,93] In a recent review, the authors concluded that the chronic exercise promotes structural and functional plasticity, improve cognition and stress coping and exert antidepressant like effects.[91] In one more review, no significant long term effects of exercise in cortisol resting levels were found.[94] Acute exercise serves as a stressor while regular exercise initiates neuroprotective effects[95] as evidenced by reduction in response to both PE and other forms of stressor challenge.[93,96] In a study, subjects assigned to an exercise program showed reduction in the depressive scores and 24-h urinary cortisol.[97] It is evident from previous studies, that antidepressant effects of exercise might be exerted through a normalization of the HPA axis.[40,98,99] However, further research is needed in this area.

### 4.4. Possible involvement of endocannabinoid system

The positive effects of endocannabinoid system on depression are well known and are partly mediated through its action on neurotrophins such as BDNF. The endocannabinoid system is one of the mechanisms involved in mediating beneficial antidepressant effects of exercise.[100] In a study involving 11 healthy trained male cyclists, exercise was found to increase the plasma levels of endocannabinoids (anandamide, AEA) and BDNF. The AEA and BDNF concentrations were positively correlated at the end of exercise and after the 15 min recovery, suggesting the possible involvement of AEA increment in exercise induced increase in peripheral BDNF levels.[100] Exercise is known to increase the levels of cortisol[91–93] and corticosteroids are known to stimulate endocannabinoid biosynthesis.[100] An increase in the serum cortisol level was also observed after intense exercise, which even continued during recovery period and it was hypothesized that this increase in cortisol might have stimulated the production of AEA.[100]

### 4.5. Effect on growth factors

Other possible mechanisms by which exercise might exert its beneficial antidepressant action might be through its effects on growth hormone (GH), insulin like growth factor-1 (IGF-1). GH and IGF-1 are responsible for regulation of many functions of central nervous system (CNS), including sleep, cognition, mood and neuroprotection.[101] Both GH and IGF-1 play a critical role in neural development and regulate size, morphology and function of CNS cells.[102] Exercise stimulates GH secretion, and both aerobic and resistance exercise result in significant acute increase in GH secretion.[103] After an acute bout of exercise, significant increase in GH levels was observed among patients with MDD.[104,105] A review found that exercise promotes a moderate increase in GH in acute studies.[94] The results of a study demonstrated that peripheral IGF-1 contributed to the antidepressant-like behavioural effect of chronic exercise in a rodent model and a role for IGF-1 in the antidepressant effect of exercise.[106] In another rodent model, central administration of IGF-1 was found to decrease depressive like behaviour and was attributed to its anti-inflammatory action.[107] However in one study in patients with MD, no significant changes in IGF-1 level was found post an aerobic exercise intervention.[108]

## 5. Summary and conclusion

A lot of research has been carried out to investigate exercise as preventative, early intervention and as a treatment option in depression. The review highlights the beneficial effects of exercise in depression. The review supports the role of exercise both as augmentative therapy as well as stand-alone treatment and in decreasing postpartum depressive symptoms. In patients performing regular exercise, the dose of antidepressant medication can be lowered. The consistency is the key factor regardless of the frequency or duration of exercise as long as exercise of moderate intensity is performed.[50] The exercise should be recommended for patients with depression though of a short duration.[52] The emphasis should be given on arranging customized exercise programs keeping in mind patient's health status and preferences for exercise regimens thereby enhancing participation rate.[109] And moreover, the exercise programs should be carried out under the supervision of professionals with relevant training. In a recent meta-analysis, supervised interventions were found to be linked with larger effects. Exercise supervised by physical educators, physiotherapists and exercise physiologists, was associated with the greatest improvements.[27] In a recent finding, the exercise interventions delivered by exercise professionals had showed lower dropout rates. The most common menace associated with exercise is increased risk of musculoskeletal injury. But still in most adults, benefits of exercise outweigh the risks. However, exercise related risks can be reduced or avoided when exercise is performed in consultation with well-trained professionals.[22] Adverse events are remarkably rare in studies evaluating exercise for depression. The patients should be advised to go with an agreeable form of exercise which suits patient rather than something

stigmatizing or stressful.[109,110] The mechanisms underlying the beneficial effect of exercise in depression are still not very well understood. However, exercise is known to induce both acute and chronic responses, particularly on hormones, neurotrophines and inflammation biomarkers in short term.[94] The main limitations of this review is that only studies involving patients with diagnosis of depression were included and studies wherein depression was reported as co-morbidity along with another disease were excluded from the review. Apart from this, there were no specific inclusion and exclusion criterions being set. In general, the effect of exercise on depression was reviewed with no specific emphasis on any particular type of exercise. The article provides brief information. Throughout the search, no specific study in Saudi population evaluating the effects of exercise as a treatment in patients diagnosed with depression was found. However, there were two studies which evaluated the effect of exercise intervention on depression scores in female university students and university employees. But it was not evident if the participants were diagnosed with depression before their enrolment or had any history of depression. The depression was one of the parameters that were being evaluated. In both the studies, a significant improvement in depression was noted post exercise intervention.[111,112] We strongly recommend that studies to evaluate the effect of exercise as a treatment modality for depression should be undertaken in Saudi population. The conclusion is that exercise should be recommended for people with mild to moderate depression based on their health status and who are motivated enough. The further research should be carried out in a larger sample size with adequate allocation concealment, using intention-to-treat analysis, using blinded outcome assessments and concentrated on ideal frequency, duration, intensity and type of exercise and identifying and studying the mechanistic pathways.

## Disclosure

The author declared that there is no conflict of interest.

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